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Unravelling the Mechanism of the Ru/C-Catalysed Isohexide and Ether Isomerization by Hydrogen Isotope Exchange

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Abstract. In this article we show that the catalytic isomerization of isohexide sugar alcohols as well as their respective ethers can occur by a hydride-based mechanism rather than a dehydrogenation/hydrogenation. C–H bonds in α-position to hydroxy and ether groups are activated using Ru/C as solid catalyst at temperatures as high as 160 °C and above. Hydrogen isotope exchange experiments proved that a full hydride exchange and isomerization is possible for isohexides but unexpectedly also for their methyl ethers. This is of great importance as it proves the co-existence of the both mechanisms for reactions that were so far assumed to occur solely by a dehydrogenation/re-hydrogenation. Hence, this co-existence should be taken into account for kinetic investigations of such reaction systems especially in the conversion of biomass-based chemicals under hydrogenation conditions.

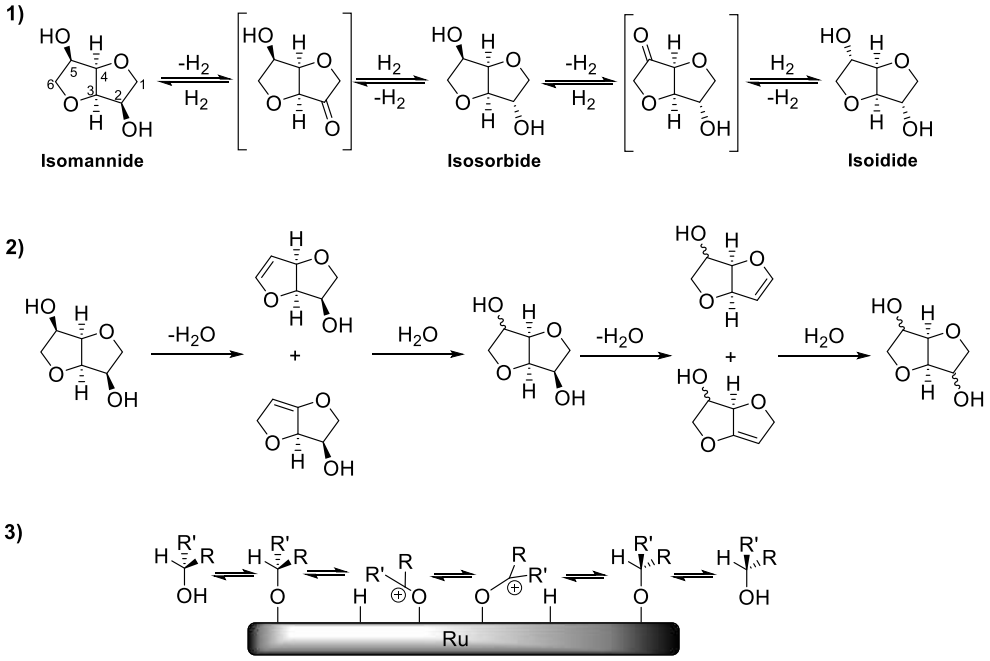
Keywords: Isomerisation; Hydrogen Isotope Exchange; Ru/C; Isohexide; Isohexide Ether

Introduction

The catalytic isomerization of biogenic platform chemicals enables a high structural and chemical diversity for the utilization of renewable resources from rare fine chemicals to bulk chemical production. Especially sugar alcohols such as glycerol, xylitol and sorbitol are considered amongst the most important renewable platform chemicals.[1] While aldose and ketose sugars are preferentially isomerised using bases or Lewis acids as catalysts[2] also metal catalysts operating under hydrogenation or hydrogenolysis conditions are reported for the isomerisation of carbohydrates.[3] The same holds true for sugar alcohols such as sorbitol or mannitol[4] as well as for isohexides as their major dianhydro derivatives.[5] Isohexides are a group of three isomers: isosorbide, isomannide, and isoidide. They are bicyclic dianhydro-diols of sorbitol, mannitol, and iditol, respectively.[6] These diols and their derivatives have been proven to be highly promising monomers for bio-based polyesters and other polymers.[7] Especially isoidide that has two *exo*-configured hydroxy groups exhibits the least sterical hindrance and thus, enables the formation of polymers with the highest molecular weights in contrast to the other two isomers.[7] However, isoidide is the only isohexide that cannot be produced from renewables in significant amounts since its precursor L-iditol is not very abundant. Therefore, the production of isoidide through isomerization of isomannide or isosorbide is considered a suitable alternative and has been reported in the past.[5c, 8] In fact, the isomerization is already known since the 1940s using heterogeneous nickel catalysts.[5a, 5b] Recently, the isomerization of isosorbide was reported by Le Nôtre *et al.* using a solid ruthenium catalyst.[5c, 8] The reaction is limited by a thermodynamic equilibrium in which the isomers are formed in a ratio of approximately 5:40:55 for isomannide, isosorbide, and isoidide, respectively. The reaction can be carried out in aqueous solutions and it was shown that the presence of hydrogen is essential for the reaction to occur. On the other hand, no hydrogen is required when using a molecular Ru catalyst.[9]

The isomerization of sugar alcohols under catalytic hydrogenation conditions is discussed in literature to proceed *via* a dehydrogenation/re-hydrogenation mechanism.[4] However, for the isomerization of isohexides there are so far three feasible mechanisms mentioned in the literature (Scheme 1):

1. dehydrogenation/re-hydrogenation mechanism *via* a ketone intermediate.[5]
2. dehydration/re-hydration mechanism.[5c]
3. direct hydride abstraction and re-addition.[5b]



Scheme 1. Feasible mechanisms for the isomerization of isohexides: 1) dehydrogenation/re-hydrogenation, 2) dehydration/re-hydration (no side reaction are displayed), 3) direct hydride abstraction and re-addition.

The dehydrogenation/re-hydrogenation mechanism is so far the most discussed mechanism in literature (Scheme 1 top). It proceeds *via* the formation of the respective ketone as intermediate. In case of molecular Ru catalysts in the absence of molecular hydrogen a hydrogen autotransfer mechanism also known as "borrowing hydrogen" concept is assumed.[10] Although for simple substrates such as cyclohexanol the respective ketone cyclohexanone can be observed in small amounts[11] the ketone intermediates were never observed in case of the isohexides.[5] Le Nôtre *et al.* discussed additionally the second option, the dehydration/re-hydration mechanism (Scheme 1, middle).[5c] However, the authors dismissed this pathway because of the absence of corresponding by-products such as unsaturated isohexide derivatives, derivatives with the hydroxy group in position 1 or 6, or without one or even both hydroxy groups. The third possibility, the direct hydride abstraction, was only mentioned once as an alternative mechanism since it could not yet be ruled out completely (Scheme 1, bottom).[5b]

For a detailed mechanistic investigation the labelling of substrates with deuterium is known to be a useful tool. Deuterium oxide is a convenient deuterium source in combination with molecular hydrogen when a metal catalyst such as Pd/C is applied.[12] Under those conditions the molecular hydrogen and the deuterium oxide undergo an exchange that results in chemisorbed deuterium on the surface and molecular deuterium in the reaction system. Moreover, also the direct exchange of a deuteron from deuterium oxide with a proton of a compound was suggested by Sajiki and co-worker, although, in these cases low pressures of molecular hydrogen are required as well.[13] The authors propose that the role of hydrogen is to activate the metal catalyst, in this case also a ruthenium species. Sajiki and co-worker investigated the catalytic H-D exchange of different molecules such as alkanes,[13a] alcohols,[14] and sugar derivatives[13b] using solid Pd, Rh, Pt, or Ru catalysts.[15] Furthermore, also unsupported Ru nanoparticles have been used to catalyse deuterium labelling.[16]

Using Ru/C as catalyst a regioselective deuteration of alcohols and sugar derivatives is possible.[13b, 17] Yet, milder conditions of 50 to 80 °C and 1 atm hydrogen pressure were applied for 24 h. In this case only the hydrogen atoms of the hydroxy substituted carbon atoms are exchanged while hydrogen atoms of the backbone or at carbon atoms with an ether group are not reactive. For simple aliphatic alcohols the authors suggest a dehydrogenation/re-hydrogenation mechanism[14] but a direct C-H activation for complex alcohols like sugar derivatives, because the sugars never epimerized due to the unfavourable steric strain of the corresponding ketone.[17] The direct C–H activation is also the proposed mechanism for the H-D exchange of alkanes.[13a]

In order to answer the two questions: 1) about the mechanism of the isomerization of isohexides and similar sugar alcohols in general and 2) the question why hydrogen is required when applying solid catalysts, we investigated the isomerization reaction using a solid ruthenium catalyst by means of a hydrogen isotope exchange study.

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Results and Discussion

The catalytic isomerization was studied using a solid ruthenium catalyst and followed by deuterium labelling with deuterium oxide as the source. First of all, we found that by using a commercially available Ru/C catalyst the isomerization equilibrium (normalized ratio of IM:IS:II of approximately 5:40:55) can be reached already in 165 min at much lower reaction temperatures of only 160 °C and 25 bar of initial hydrogen pressure (at 25 °C) instead of the ≥200 °C and 40-250 bar as stated in the literature.[5] A concentration-time-profile for the isomerization of isosorbide at 160 °C is displayed in the supporting information (Figure S1a). These conditions were then chosen for the deuterium labelling experiments as the isomerization proceeds to a very similar extend (Figure S2).

If a dehydrogenation/re-hydrogenation mechanism is assumed only the protons of the hydroxy groups as well as the protons at the hydroxyl-substituted carbon atoms (position 2 and 5) are expected to be exchanged. After a reaction time of 3 h and temperatures as high as 160 °C all signals of the isohexides vanished in the ^{1}H NMR spectrum (Figure 1). Thus, all protons of the isohexide backbone are exchanged by deuterium. This is in contrast to the literature results with alcohols and sugar molecules as reagents as only the hydrogen atoms in α-position to hydroxy groups are expected to be exchanged. However, in comparison we are working at much higher temperatures. In fact, with 160 °C the reaction temperature is in the same range as in the literature reports in which even the deuteration of alkanes was possible.[13a] Beside 160 also 120 and 80 °C were screened (Figure 1). After 3 h reaction time at 80 °C neither isomerization nor deuterium exchange activity could be observed. At 120 °C the isomerization already started but has yet not reached the

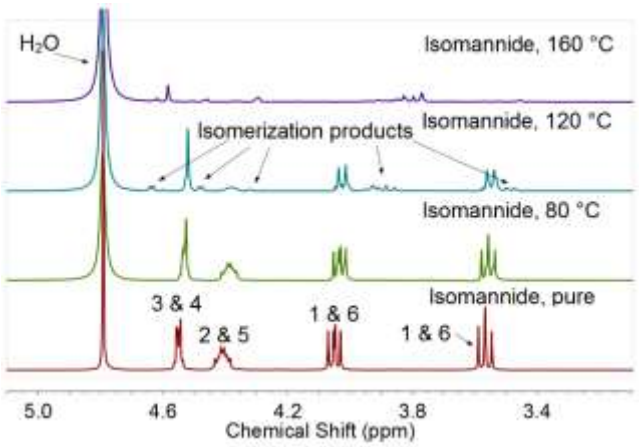
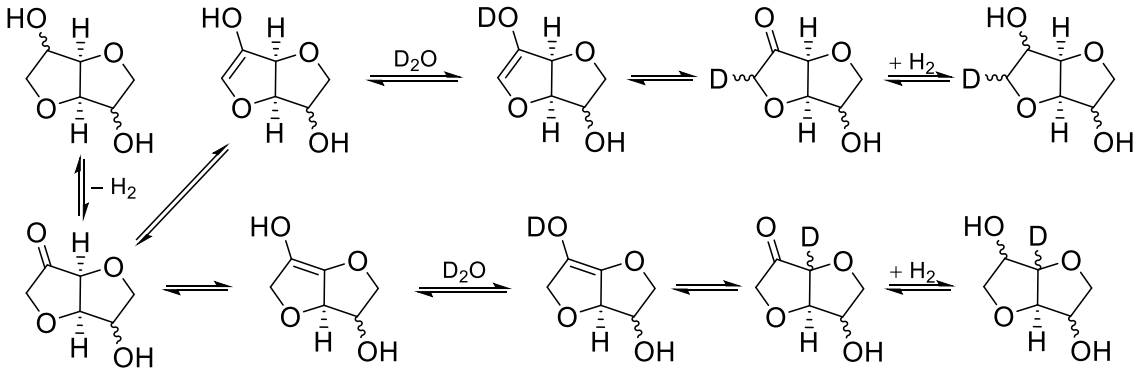


Figure 1. ^{1}H NMR (close-up) of pure isomannide as well as of the product solutions after isomerization at the indicated temperatures for 3 h. D_2O was used as the solvent and the deuterium source. The numbers depict the corresponding carbon atom number.

equilibrium since the reaction rate is much lower at lower temperatures. In the isomerization of isosorbide at 120 °C the normalized ratio of the isohexides after 3 h is 1:96:3 (IM:IS:II). A corresponding concentration-time-profile can be found in the supporting information (Figure S1b) for better clarity.

The deuterium exchange can be observed at 120 °C although to a lesser extent. Especially, the hydrogen atoms attached to the carbon atoms bearing the hydroxy group disappear in the ^{1}H NMR spectrum. This shows that the protons at position 2 and 5 are preferentially exchanged, indicating a dehydrogenation/re-hydrogenation mechanism at this temperature. Furthermore, in the absence of molecular hydrogen no H-D exchange is witnessed. This is in accordance to the literature.[15a]



Scheme 2. Feasible route for a complete deuterium exchange through a keto-enol tautomerization after the dehydrogenation step.

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The overall H-D exchange of the isohexides at 160 °C can be explained by two possible pathways: 1) keto-enol tautomerization after the dehydrogenation step (Scheme 2) or alternatively 2) by a C–H bond activation as proposed by Sajiki and co-workers for alkanes.[13a] Considering the latter route, the isomerization of the isohexides could also proceed by C–H activation under these conditions (Scheme 1, bottom). In this case the molecule is bound with the oxygen of the hydroxy group to the ruthenium surface which is known to be highly oxophilic.[18] Then a heterolytic cleavage of the C–H bond results in a prochiral carbenium ion and a surface hydride.

Although also a homolytic cleavage of the C–H bond is possible, working in the protic environment of water, a heterolytic cleavage is more likely. The carbenium ion can than rotate along the C–O bond as well as the Ru–O bond. Thus, an inversion of the stereo centre can be obtained providing that an additional surface hydride is available for the isomerization. This explains the need of additional molecular hydrogen although it is overall not consumed in the reaction. The dehydrogenation/re-hydrogenation mechanism can occur in a similar way but the ketone intermediate is formed which can desorb from the catalyst's surface as mentioned in the literature[4b] in contrast to the direct C–H activation as a concerted mechanism that would not result in a stable intermediated that could desorb.

In order to elucidate whether the isomerization as well as the H-D exchange proceeds solely through a dehydrogenation/re-hydrogenation (for the deuterium exchange with keto-enol tautomerization as intermediate step) experiments with dimethyl isosorbide (DMI) instead of the free sugar alcohol were performed. First, the mere isomerization was investigated. Thus, the reaction was performed in water instead of deuterium oxide. Although one would expect no isomerization to occur, a broad product spectrum was obtained. By GC-MS approximately half of the products could be identified (Figure S7-S20). Besides residual DMI, the monoethers were the main products and also one isohexide, most likely isosorbide, could be detected. Consequently, ether cleavage by hydrogenolysis occurs to a large extend. Since methane was detected in the gas phase via GC, the cleavage proceeds through a hydrogenolysis of the C-O bonds. Interestingly, three monoethers could be identified as well. However, DMI itself can only be cleaved into two different monoethers in case solely hydrogenolysis occurs. Therefore, they have to be formed partially by isomerization. It could not be identified whether the isomerization happened at the ether or the hydroxy moiety. Although the isomerization at the hydroxy group is more likely, the

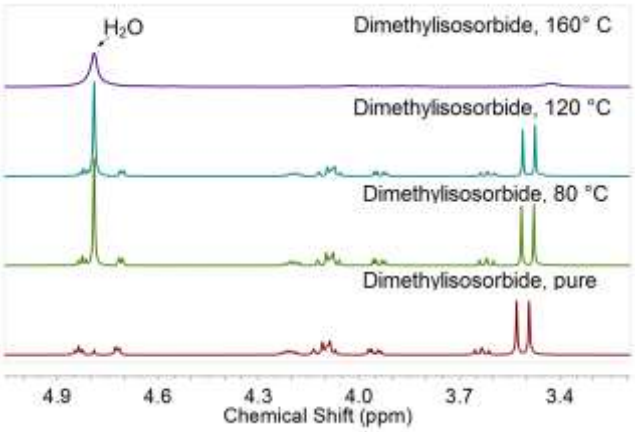

Figure 2. ^{1}H NMR (close-up) of pure dimethyl isosorbide (DMI) as well as of the product solutions after isomerization at the indicated temperatures for 3 h. D_2O was used as the solvent and the deuterium source.

isomerization at the ether group cannot be ruled out. Furthermore, a compound possessing the same molar mass as DMI could be identified in the product spectrum. A re-etherification after the cleavage by hydrogenolysis that forms methane and subsequent isomerization is highly unlikely. Hence, DMI itself had to be isomerized as well. This cannot be explained by a mere dehydrogenation/re-hydrogenation mechanism due to the ether functionalities that cannot be dehydrogenated. Thus, a direct hydride exchange has to be involved. The mechanism can be assumed in analogy to the aforementioned C–H activation mechanism for the isomerization of isohexides via a carbenium ion (Scheme 3). Therefore, the general isomerization is not only possible via dehydrogenation/re-hydrogenation but also by a direct C–H activation at temperatures of at least 160 °C.

In the literature almost no H-D exchange was observed at carbon atoms bearing an ether functionality using a Pd/C catalyst.[19] Since we observed isomerization of DMI under the applied conditions, also the H-D exchange was investigated using DMI as substrate and Ru/C as catalyst. Again without molecular hydrogen present only DMI could be detected in the NMR as well as by HPLC analytics. For the reactions with molecular hydrogen 80, 120 and 160 °C were screened as reaction temperatures. While at the first two temperatures no changes in the ^{1}H NMR spectrum (Figure 2) could be observed, basically all signals vanished at 160 °C.

Interestingly, since methoxy groups were cleaved only partially by hydrogenolysis, also the signals for the terminal methyl group at the ether moiety vanished because of H-D exchange. Thus, with a Ru/C catalyst, higher hydrogen pressure as well as higher temperatures a full H-D exchange is possible

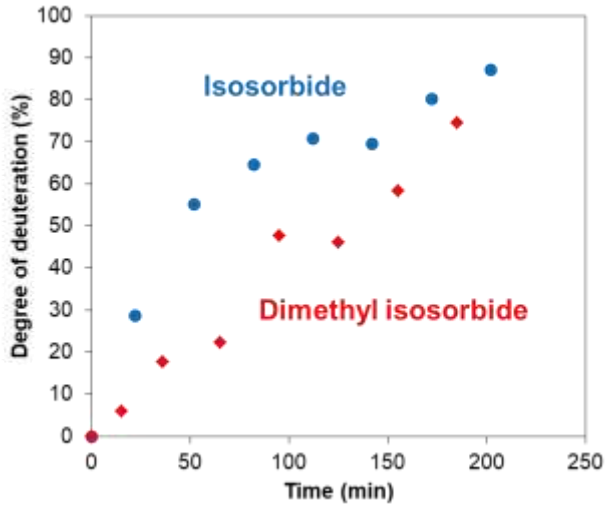

Figure 3. Time resolved H-D exchange profile starting from isosorbide and dimethyl isosorbide at 160 °C.

even in α-positions to all ether moieties in DMI. In contrast to the full deuterium exchange in the isohexides, the complete deuteration of especially DMI and its observed isomer cannot be explained by keto-enol tautomerization. Therefore, the deuterium exchange has to proceed through a direct C–H activation. Additional hydrogen is required to ensure a certain surface coverage of the active metal surface for the hydride addition towards the isomeric species.

For a direct comparison of the isomerization reaction and the H-D exchange additional time-resolved experiments were conducted using the same Ru/C catalyst as in the experiments above. The isomerization of isosorbide at 160 °C (Figure S1) shows that half and full equilibrium composition are obtained after approximately 30-40 and 120 min, respectively. On the other hand, the H-D exchange experiments starting from isosorbide and dimethyl isosorbide, respectively, show overall similar reaction kinetics compared to the isomerization reaction (Figure 3 and S5, S6).

Although the H-D exchange was quantified by quantitative ^{1}H NMR spectroscopy with a certain error a clear trend is obvious: The H-D exchange is significantly faster for isosorbide than for dimethyl isosorbide. This indicates that the H-D exchange with free hydroxyl groups is faster since it can progress via the dehydrogenation/re-hydrogenation with an exchange of all hydrogen atoms due to keto-enol tautomerization. Nevertheless, the exchange also occurs for dimethyl isosorbide which further proves that the mechanism which is responsible for the C–H activation and the H-D exchange is probably also involved in the isomerization reaction. Hence, not only the dehydrogenation/re-hydrogenation has to be considered but rather also a direct C–H activation-based mechanism that occurs in parallel.

Conclusion

In conclusion we were able to demonstrate the existence of an alternative mechanism to the dehydrogenation/re-hydrogenation mechanism that is typically assumed for the isomerization of sugar alcohols such as isohexides. At temperatures ≥160 °C the activation barrier for a direct C–H bond activation can be overcome and a direct hydride exchange is enabled as a feasible alternative mechanism which also allows ether derivatives to be isomerized. Furthermore, the C–H activation facilitates a complete deuterium exchange of not only the whole isohexide backbone but also of the methoxy groups of their ether derivatives. Hence, this should enable the direct isomerization of asymmetric ethers instead of only alcohols. More importantly it proves the co-existence of the two different mechanisms and renders a treatment of the reaction kinetics based solely on the dehydrogenation/re-hydrogenation mechanism obsolete and probably insufficient.

Experimental Section

A full description of the experimental details can be found in the supporting information. In short the procedure for the catalytic hydrogen isotope exchange experiments was as follows: In a 45 mL autoclave, isomannide (1.50 g, 10.3 mmol) was dissolved in D_2O (5 g) and 1 mol-% of a 5 wt.% Ru/C were added. The closed autoclave was pressurized with 25 bar hydrogen (at RT). The reaction mixture was stirred using a magnetic stirring bar for 3 h at temperatures between 80-160 °C. Afterwards the autoclave was cooled to room temperature using an ice bath. Subsequently the solid catalyst was filtered off and a sample was analysed using HPLC and quantitative ^{1}H NMR spectroscopy.

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